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(54) 4-Substituted-2-hydroxybutanoates and a process for producing them

4-Substituierte-2-hydroxybutanoate und ein Verfahren zu ihrer Herstellung

2-Hydroxybutanoates substitués en 4 et un procédé pour leur préparation

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(56) References cited:
GB-A- 2 132 614 **US-A- 4 495 190**

- **JACS, April 1937, p.753-759**
- **EP-A 0 381 984**

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Description

The present invention relates to a process for producing optically active 4-substituted-2-hydroxybutanoates which are useful chemical compounds as starting materials of medical supplies.

Optically active 4-substituted-2-hydroxybutanoates of the present invention are useful for starting materials of many medical supplies. However, there was no effective process so that racemic methyl 4-chloro-2-hydroxybutanoate, racemic methyl 4-bromo-2-hydroxybutanoate and the like were used (European Patent Laid-open Application No. 233728, etc.).

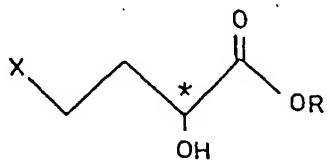
EP-A-0 381 984 discloses the conversion of a furanone with iodotrimethylsilane in an alcohol solvent at a temperature ranging from 0°C to the reflux temperature of the solvent.

A paper by J. W. E. Glattfeld and A. M. Stack (JACS, 1937, pages 753 to 759) relates to 3-hydroxy and 2-hydroxy butyrolactone and its conversion with a HCl containing ethanol solution to ethyl 3-hydroxy-4-chloro-butyrate and ethyl 2-hydroxy-4-chloro-butyrate, respectively. However, the yields obtained according to this process are very low (42.9% and 32.5%).

Lately, when racemic compounds are used as medical supplies, it is necessary to examine each physiological activity of two enantiomorphs, because the physiologically activities may be different. Further, when a compound having a stereostructure especially has a strong physiological activity, it is earnestly required to construct only a compound having the desired stereostructure, considering the efficiency and safety.

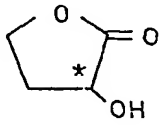
The inventors of the present invention have developed a process for producing optically active 4-substituted-2-hydroxybutanoates which become useful compounds as starting materials of pharmaceuticals,

According to the first aspect of the present invention there is provided a process for producing an optically active 4-substituted-2-hydroxybutanoate represented by the formula (Ia)



(Ia)

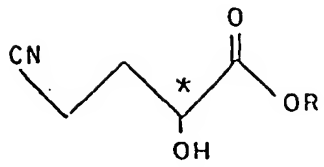
wherein X' is Cl or Br, R is alkyl of 1-10 carbon atoms, and * shows an asymmetric carbon which comprises contacting a compound of the formula:



(II)

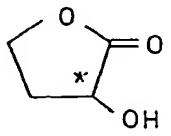
wherein * shows an asymmetric carbon with alkyl alcohol of 1-10 carbon atoms saturated with hydrogen chloride or hydrogen bromide at room temperature to perform the following reactions (1) ring-opening of the compound of the formula (II), (2) introducing a Cl ion or a Br ion derived from said hydrogen chloride or hydrogen bromide into the fourth position of thus obtained ring-opened intermediate of the compound of the formula (II) and (3) introducing an alkyl group derived from said alkyl alcohol into the carbonyloxy portion of thus obtained ring-opened intermediate of the compound of the formula (II) in one step,
blowing nitrogen gas through the resultant solution to remove hydrogen chloride gas remained therein and distilling away the alkyl alcohol.

According to the second aspect of the present invention there is provided a process for producing an optically active 4-substituted-2-hydroxybutanoate represented by the formula (Ib)



(Ib)

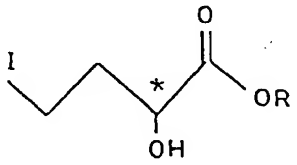
R is alkyl of 1-10 carbon atoms, and * shows an asymmetric carbon which comprises contacting a compound of the formula:



(II)

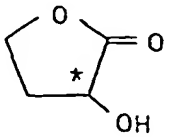
wherein * shows an asymmetric carbon, with trimethylsilyl cyanide to perform the following reactions (1) ring-opening of the compound of the formula (II), (2) introducing a CN ion derived from said trimethylsilyl compound into the fourth position of thus obtained ring-opened intermediate of the compound of the formula (II) and (3) introducing an alkyl group derived from an alkyl alcohol of 1-10 carbon atoms into the carbonyloxy portion of thus obtained ring-opened intermediate of the compound of the formula (II).

According to the third aspect of the present ivention there is provided a process for producing an optically active 4-substituted-2-hydroxybutanoate represented by the formula (Ic)



(Ic)

wherein R is alkyl of 1-10 carbon atoms, and * shows an asymmetric carbon which comprises contacting a compound of the formula:



(II)

wherein * shows an asymmetric carbon with trimethylsilyl chloride and sodium iodide in a solvent to perform the following reactions (1) ring-opening of the compound of the formula (II) and (2) introducing a I ion derived from said sodium iodide into the fourth position of thus obtained ring-opened intermediate of the compound of the formula (II), and contacting the thus obtained I ion introduced ring-opened intermediate with an alkyl alcohol of 1-10 carbon atoms to introduce an alkyl group derived from said alkyl radical into the carbonyloxy portion of said I ion introduced ring-opened intermediate.

The following description illustrates this invention more specifically.

Optically active 4-substituted-2-hydroxybutanoates produced in the process of the present invention are represented by the above general formulae Ia, Ib and Ic. As these compounds, the following compounds are exemplified:

R-methyl 4-chloro-2-hydroxybutanoate,
R-ethyl 4-chloro-2-hydroxybutanoate,

R-propyl 4-chloro-2-hydroxybutanoate,
R-butyl 4-chloro-2-hydroxybutanoate,
R-pentyl 4-chloro-2-hydroxybutanoate,
S-methyl 4-chloro-2-hydroxybutanoate,
S-ethyl 4-chloro-2-hydroxybutanoate,
S-propyl 4-chloro-2-hydroxybutanoate,
S-butyl 4-chloro-2-hydroxybutanoate,
S-pentyl 4-chloro-2-hydroxybutanoate,
R-methyl 4-bromo-2-hydroxybutanoate,
R-ethyl 4-bromo-2-hydroxybutanoate,
R-propyl 4-bromo-2-hydroxybutanoate,
R-butyl 4-bromo-2-hydroxybutanoate,
R-pentyl 4-bromo-2-hydroxybutanoate,
S-methyl 4-bromo-2-hydroxybutanoate,
S-ethyl 4-bromo-2-hydroxybutanoate,
S-propyl 4-bromo-2-hydroxybutanoate,
S-butyl 4-bromo-2-hydroxybutanoate,
S-pentyl 4-bromo-2-hydroxybutanoate,
R-methyl 4-iodo-2-hydroxybutanoate,
R-ethyl 4-iodo-2-hydroxybutanoate,
R-propyl 4-iodo-2-hydroxybutanoate,
R-butyl 4-iodo-2-hydroxybutanoate,
R-pentyl 4-iodo-2-hydroxybutanoate,
S-methyl 4-iodo-2-hydroxybutanoate,
S-ethyl 4-iodo-2-hydroxybutanoate,
S-propyl 4-iodo-2-hydroxybutanoate,
S-butyl 4-iodo-2-hydroxybutanoate,
S-pentyl 4-iodo-2-hydroxybutanoate,
R-methyl 4-cyano-2-hydroxybutanoate,
R-ethyl 4-cyano-2-hydroxybutanoate,
R-propyl 4-cyano-2-hydroxybutanoate,
R-butyl 4-cyano-2-hydroxybutanoate,
R-pentyl 4-cyano-2-hydroxybutanoate,
S-methyl 4-cyano-2-hydroxybutanoate,
S-ethyl 4-cyano-2-hydroxybutanoate,
S-propyl 4-cyano-2-hydroxybutanoate,
S-butyl 4-cyano-2-hydroxybutanoate,
S-pentyl 4-cyano-2-hydroxybutanoate and the like.

The optically active 4-substituted-2-hydroxybutanoates of the present invention are obtained by ring-opening optically active α-hydroxy-γ-butyrolactone represented by the above formula (II) which is obtained by optically cally resolution wherein racemic α-hydroxy-γ-butyrolactone is transesterified with ethyl acetate, a fatty acid vinyl ester, a triglyceride or the like in the presence of an esterase produced by a microorganism or an esterase from an animal as a catalyst, and esterifying the compound obtained.

The racemic α-hydroxy-γ-butyrolactone of a raw material can be easily obtained from a-bromo-y-butyrolactone by a method of Goal et al. (Organic Preparations and Procedures Int., 17, 91 (1985)).

As fatty acid vinyl esters used in the transesterification reaction, vinyl acetate, vinyl propionate, vinyl butyrate, vinyl caproate, vinyl laurate, etc. can be used. As triglycerides, triacetin, tripropionin, tributyrin, tricaproin, trilaurin etc. can be exemplified. These compounds are commercially available without any difficulty.

The following table shows commercially available esterases.

Table

Trade name	Origin	Seller or Maker
Lipase PS	Pseudomonas sp	Amono Pharmaceutical Co.,Ltd
Lipase CES	Pseudomonas sp	"
Lipase AP	Aspergillus niger	"
Lipase M	Mucor javanicus	"
Lipase CE	Humicola lanuginosa	"
Lipase F-AP	Rhizopus javanicus	"
Lipase II	Porcine Pancreas	Sigma Chemical Co.,Ltd
Lipase VIII	Geotrichum Candidum	"
Lipase X	Rhizopus delamar	"
Lipase	Chromobacterium Viscosum	Toyo Jozo Co.,Ltd
Lipase A	Aspergillus niger	Novo Industi A/S
Lipase	Rhizopus niveus	Nagase Biochemicals, Ltd.
Lipase B	Pseudomonas fragi	Sapporo Beer Co.

In addition to these esterases, the enzymes produced from microorganisms can be used. These microorganisms which produce the enzymes having the above reaction ability can be used regardless of their species and genus. As such microorganisms, the genera Pseudomonas, Arthrobacter, Acromobacter, Alcaligenes, Aspergillus, Chromobacterium, Candida, Mucor, Rhizopus, etc. can be exemplified.

In these microorganisms, particularly the genus Pseudomonas is preferred.

The transesterification reaction is conducted by mixing a racemic α-hydroxy-γ-butyrolactone with ethyl acetate, a fatty acid vinyl ester or a triglyceride and by efficiently contacting the mixture with an esterase. The reaction temperature is suitably from room temperature (about 10°C) to 150°C, especially and preferably from 20 to 45°C. The reaction time is from 1 to 1000 hours. α-hydroxy-γ-butyrolactone and ethyl acetate, the fatty acid vinyl ester or the triglyceride are suitably mixed in the ratio from 1:0.5 to 1:10 by mole, preferably 1:0.5 by mole.

When necessary, n-hexane, n-heptane, benzene, toluene, ethyl ether, etc. can be used as a solvent by which esterase activity is not inhibited. The solvent may be unused.

After the transesterification reaction is conducted, the esterase can be removed by conventional filter operation and used again, as it is. After concentrating the filtrate, optically active α-hydroxy-γ-butyrolactone and an optically active α-acyloxy-γ-butyrolactone can be separated by vacuum distillation or column chromatography, respectively. When these lactones have insufficient optical purities, each lactone is re-transesterified (in the case of the acyl compound, after the acyl group is hydrolyzed) to obtain a high optically pure compound.

The optically active α-hydroxy-γ-butyrolactone obtained can lead to the production of optically active 4-chloro-3-hydroxybutanoate or optically active 4-bromo-3-hydroxybutanoate by reaction with ethyl alcohol saturated with hydrogen chloride or hydrogen bromide.

Further, optically active α-hydroxy-γ-butyrolactone can lead to the production of optically active 4-iodo-2-hydroxybutanoate by reaction with trimethylsilyl chloride and sodium iodide or trimethylsilyl iodide.

Moreover, optically active α-hydroxy-γ-butyrolactone can lead to the production of optically active 4-cyano-2-hydroxybutanoate by reaction with trimethylsilylcyanide. Otherwise, it can lead to the production of optically active 4-cy-

ano-2-hydroxybutanoate by cyanizing optically active 4-halo-2-hydroxybutanoate.

By using the above operation, R- and S-compound of optically active 4-substituted-2-hydroxybutanoate can be obtained, respectively.

Optically active 4-substituted-2-hydroxybutanoates of the present invention are useful and applicable compounds for starting materials of medical supplies. For example, optically active guanine derivatives (United States Patent Application US 4495190 etc.) which are useful for physiologically active materials can be obtained. Otherwise, as to calcium channel blockers (Japanese Patent Laid-open Application No. 61-87503, etc.), optically active materials by which more effective activity is expected can be obtained.

The following examples illustrate the present invention tion more specifically, but these will not always be precise in practical applications.

Example 1

(i) Production of R-(+)-α-hydroxy-γ-butyrolactone

A mixture of 15.3 g of racemic-α-hydroxy-γ-butyrolactone, 6.5 g of vinyl acetate and 5 g of lipase PS (manufactured by Amano Pharmaceutical Co., Ltd.) was put into a 100 ml flask. The mixture was stirred for 6 hours at room temperature. After lipase PS was removed by filtration, the filtrate was concentrated and about 40 g of liquid was obtained. The liquid was column-chromatographed (toluene/ethyl acetate (10/1)), and 5.2 g of S-(-)-α-hydroxy-γ-butyrolactone ($[\alpha]_D$ -57.6° (c 1.22, $CHCl_3$), 99%ee) and 7.2 g of R-(+)-α-acetyloxy-γ-butyrolactone ($[\alpha]_D$ +32.6° (c 0.87, $CHCl_3$), 70%ee) were separated, respectively.

R-(+)-α-acetyloxy-γ-butyrolactone was dissolved into a mixed solvent of 50 ml of 1,4-dioxane and 30 ml of ethanol, and 3.8 g of potassium carbonate was added. The mixture was stirred for 5 hours at room temperature. After the mixture was neutralized with hydrochloric acid, the salt separated was removed by filtration. Moreover, after removing ethanol, the filtrate was purified by distillation, and 6.1 g of R-(+)-a-hydroxy-y-butyrolactone was obtained.

(ii) Production of R-ethyl (+)-4-chloro-2-hydroxybutanoate

1.6 g of R-(+)-α-hydroxy-γ-butyrolactone (90%ee) was dissolved into 200 ml of ethanol, and the solution was put into a 300 ml three-necked flask. Hydrogen chloride gas was blown into the three-necked flask, and the solution was stirred in a saturated condition at room temperature overnight. After hydrogen chloride gas was removed thoroughly by blowing nitrogen through the solution, ethanol was distilled away, and the residue was extracted with ether. The ether layer was washed with sodium bicarbonate and then with a saturated saline solution. After the ether layer was dried on anhydrous magnesium sulfate, ether was distilled away. The residue was distilled under reduced pressure to obtain 2.1 g of the desired R-ethyl (+)-4-chloro-2-hydroxybutanoate. The physical properties of the compound are as follows.

Boiling point:	112°C/17 mmHg
Specific rotation:	$[\alpha]_D$+6.1° (C1.9, $CHCl_3$)

Example 2

Production of S-ethyl (-)-4-chloro-hydroxybutanoate

1.6 g of S-(-)-α-hydroxy-γ-butyrolactone (90%ee) was dissolved into 200 ml of ethanol, and the solution was put into a 300 ml three-necked flask. Hydrogen chloride gas was blown into the three-necked flask, and the solution was stirred in a saturated condition at room temperature overnight. After hydrogen chloride gas was removed thoroughly by blowing nitrogen through the solution, ethanol was distilled away, and the residue was extracted with ether. The ether layer was washed with sodium bicarbonate and then with a saturated saline solution. After the ether layer was dried on anhydrous magnesium sulfate, ether was distilled away. The residue was distilled under reduced pressure to obtain 2.0 g of the desired S-ethyl (-)-4-chloro-2-hydroxy butanoate. The physical properties of the compound are as follows.

Boiling point:	101°C/13 mmHg
Specific rotation:	$[\alpha]_D$-6.7° (C1.2, $CHCl_3$)

Example 3

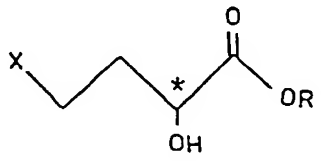
Production of R-ethyl (+)-4-iodo-2-hydroxybutanoate

20 ml of an acetonitrile solution of trimethylsilyl chloride was slowly added into 50 ml of an acetonitrile solution containing 1.3 g of R-(+)-α-hydroxy-γ-butyrolactone (70%ee) and 5.7 g of sodium iodide. After the solution was heated under reflux for 14 hours, 10 ml of ethanol was added dropwise and the solution was stirred at room temperature for 10 minutes.

Acetonitrile was distilled away, and ether was added to the residue. The ether layer was washed with sodium bicarbonate and then with a saturated saline solution. After the ether layer was dried on anhydrous magnesium sulfate, ether was distilled away. 0.73 g of the desired R-ethyl (+)-4-iodo-2-hydroxybutanoate was obtained. Specific rotation: $[\alpha]_D$+4.0° (C1.15, $CHCl_3$)

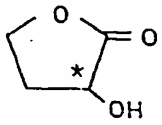
Claims

1. A process for producing an optically active 4-substituted-2-hydroxybutanoate represented by the formula (Ia)



(Ia)

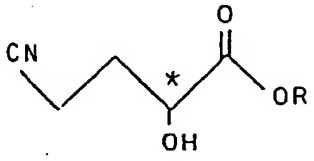
wherein X' is Cl or Br, R is alkyl of 1-10 carbon atoms, and * shows an asymmetric carbon which comprises contacting a compound of the formula:



(II)

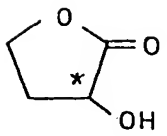
wherein * shows an asymmetric carbon with alkyl alcohol of 1-10 carbon atoms saturated with hydrogen chloride or hydrogen bromide at room temperature to perform the following reactions (1) ring-opening of the compound of the formula (II), (2) introducing a Cl ion or a Br ion derived from said hydrogen chloride or hydrogen bromide into the fourth position of thus obtained ring-opened intermediate of the compound of the formula (II) and (3) introducing an alkyl group derived from said alkyl alcohol into the carbonyloxy portion of thus obtained ring-opened intermediate of the compound of the formula (II) in one step,
blowing nitrogen gas through the resultant solution to remove hydrogen chloride gas remained therein and distilling away the alkyl alcohol.

2. A process for producing an optically active 4-substituted-2-hydroxybutanoate represented by the formula (Ib)



(Ib)

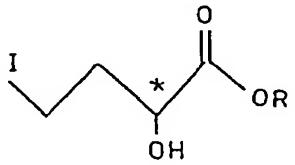
R is alkyl of 1-10 carbon atoms, and * shows an asymmetric carbon which comprises contacting a compound of the formula:



(II)

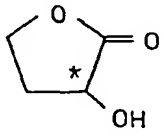
wherein * shows an asymmetric carbon, with trimethylsilyl cyanide to perform the following reactions (1) ring-opening of the compound of the formula (II), (2) introducing a CN ion derived from said trimethylsilyl compound into the fourth position of thus obtained ring-opened intermediate of the compound of the formula (II) and (3) introducing an alkyl group derived from an alkyl alcohol of 1-10 carbon atoms into the carbonyloxy portion of thus obtained ring-opened intermediate of the compound of the formula (II).

3. A process for producing an optically active 4-substituted-2-hydroxybutanoate represented by the formula (Ic)



(Ic)

wherein R is alkyl of 1-10 carbon atoms, and * shows an asymmetric carbon which comprises contacting a compound of the formula:

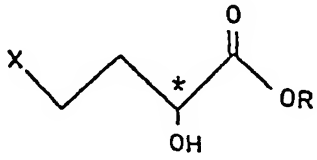


(II)

wherein * shows an asymmetric carbon with trimethylsilyl chloride and sodium iodide in a solvent to perform the following reactions (1) ring-opening of the compound of the formula (II) and (2) introducing a I ion derived from said sodium iodide into the fourth position of thus obtained ring-opened intermediate of the compound of the formula (II), and contacting the thus obtained I ion introduced ring-opened intermediate with an alkyl alcohol of 1-10 carbon atoms to introduce an alkyl group derived from said alkyl radical into the carbonyloxy portion of said I ion introduced ring-opened intermediate.

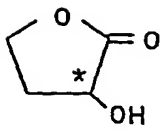
Patentansprüche

1. Verfahren zur Herstellung eines durch die Formel (Ia) dargestellten optisch aktiven 4-substituierten 2-Hydroxybutansäureesters:



(Ia)

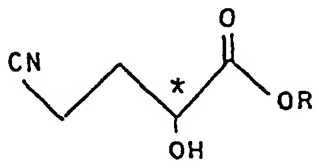
worin X Cl oder Br ist, R Alkyl mit 1 bis 10 Kohlenstoffatomen ist und * ein asymmetrisches Kohlenstoffatom anzeigt, umfassend das Kontaktieren einer Verbindung der Formel:



(II)

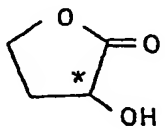
worin * ein asymmetrisches Kohlenstoffatom anzeigt, mit einem mit Chlorwasserstoff oder Bromwasserstoff gesättigten Alkylalkohol mit 1 bis 10 Kohlenstoffatomen bei Raumtemperatur, um die folgenden Reaktionen durchzuführen: (1) das Ringöffnen der Verbindung der Formel (II), (2) das Einführen eines von besagtem Chlorwasserstoff oder Bromwasserstoff stammenden Chlorions oder Bromions in die vierte Position des so erhaltenen ringgeöffneten Intermediats der Verbindung der Formel (II) und (3) das Einführen einer von besagtem Alkylalkohol stammenden Alkyl-Gruppe in den Carbonyloxy-Abschnitt des so erhaltenen ringgeöffneten Intermediats der Verbindung der Formel (II) in einem Schritt,
das Blasen von Stickstoffgas durch die resultierende Lösung, um darin verbliebenes Chlorwasserstoffgas zu entfernen und das Abdestillieren des Alkylalkohols.

2. Verfahren zur Herstellung eines durch die Formel (Ib) dargestellten optisch aktiven 4-substituierten 2-Hydroxybutansäureesters:



(Ib)

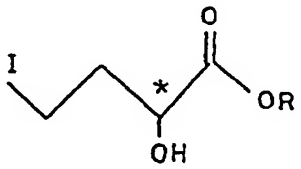
worin R Alkyl mit 1 bis 10 Kohlenstoffatomen ist und * ein asymmetrisches Kohlenstoffatom anzeigt, umfassend das Kontaktieren einer Verbindung mit der Formel:



(II)

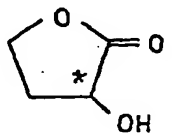
worin * ein asymmetrisches Kohlenstoffatom anzeigt,
mit Trimethylsilylcyanid, um die folgenden Reaktionen durchzuführen: (1) Ringöffnen der Verbindung der Formel (II), (2) das Einführen eines aus besagter Trimethylsilyl-Verbindung stammenden CN-Ions in die vierte Position des so erhaltenen ringgeöffneten Intermediats der Verbindung der Formel (II) und (3) das Einführen einer aus einem Alkylalkohol mit 1 bis 10 Kohlenstoffatomen stammenden Alkyl-Gruppe in den Carbonyloxy-Abschnitt des so erhaltenen ringgeöffneten Intermediats der Verbindung der Formel (II).

3. Verfahren zur Herstellung eines durch die Formel (Ic) dargestellten optisch aktiven 4-substituierten 2-Hydroxybutansäureesters:



(Ic)

worin R Alkyl mit 1 bis 10 Kohlenstoffatomen ist, und * ein asymmetrisches Kohlenstoffatom anzeigt, umfassend das Kontaktieren einer Verbindung der Formel:

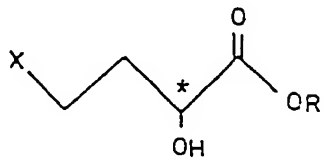


(II)

worin * ein asymmetrisches Kohlenstoffatom anzeigt,
mit Trimethylsilylchlorid und Natriumjodid in einem Lösungsmittel, um die folgenden Reaktionen durchzuführen: (1) das Ringöffnen der Verbindung der Formel (II) und (2) das Einführen eines aus besagtem Natriumjodid stammenden Jodions in die vierte Position des so erhaltenen ringgeöffneten Intermediats der Verbindung der Formel (II) und das Kontaktieren des so erhaltenen, ein eingeführtes Jodion aufweisenden, ringgeöffneten Intermediats mit einem Alkylalkohol mit 1 bis 10 Kohlenstoffatomen, um eine aus besagtem Alkyl-Rest stammende Alkyl-Gruppe in den Carbonyloxy-Abschnitt des besagten, ein eingeführtes Jodion aufweisenden, ringgeöffneten Intermediats einzuführen.

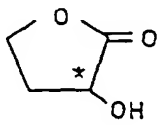
Revendications

1. Procédé pour la préparation d'un 2-hydroxybutanoate substitué en position 4 optiquement actif représenté par la formule (Ia)



(Ia)

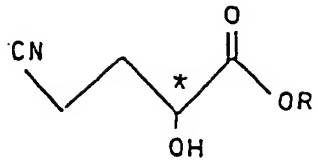
où X' est Cl ou Br, R est un goupe alkyle comportant de 1 à 10 atomes de carbone et * représente un carbone asymétrique, qui consiste à mettre en contact un composé de la formule :



(II)

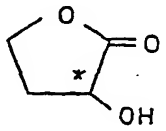
où * représente un carbone asymétrique avec un alkylalcool comportant de 1 à 10 atomes de carbone saturé avec du chlorure d'hydrogène ou avec du bromure d'hydrogène à température ambiante en vue d'effectuer les réactions suivantes : (1) ouvrir le cycle du composé de la formule (II), (2) introduire un ion Cl ou un ion Br provenant dudit chlorure d'hydrogène ou dudit bromure d'hydrogène sur la quatrième position de l'intermédiaire au cycle ouvert ainsi obtenu du composé de la formule (II) et (3) introduire un groupe alkyle provenant dudit alkylalcool dans la partie carbonyloxylée de l'intermédiaire au cycle ouvert ainsi obtenu du composé de la formule (II) en une étape,
faire passer le l'azote dans la solution qui en résulte afin d'éliminer le chlorure d'hydrogène gazeux restant dans celle-ci et éliminer l'alkylalcool par distillation.

2. Procédé pour la préparation d'un 2-hydroxybutanoate substitué en position 4 optiquement actif représenté par la formule (Ib)



(Ib)

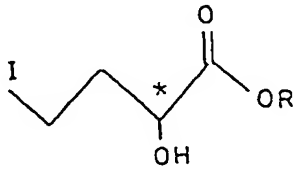
où R est un groupe alkyle comportant de 1 à 10 atomes de carbone et * représente un carbone asymétrique, qui consiste à mettre en contact un composé de la formule :



(II)

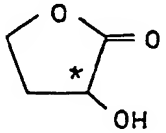
où * représente un carbone asymétrique, avec du cyanure de triméthylsilyle en vue d'effectuer les réactions suivantes: (1) ouvrir le cycle du composé de la formule (II), (2) introduire un ion CN provenant dudit composé triméthylsilyle sur la quatrième position de l'intermédiaire au cycle ouvert ainsi obtenu du composé de la formule (II) et (3) introduire un groupe alkyle provenant d'un alkylalcool comportant de 1 à 10 atomes de carbone dans la partie carbonyloxylée de l'intermédiaire au cycle ouvert ainsi obtenu du composé de la formule (II).

3. Procédé pour la préparation d'un 2-hydroxybutanoate substitué en position 4 optiquement actif représenté par la formule (Ic)



(Ic)

où R est un groupe alkyle comportant de 1 à 10 atomes de carbone et * représente un carbone asymétrique, qui consiste à mettre en contact un composé de la formule :



(II)

où * représente un carbone asymétrique, avec du chlorure de triméthylsilyle et de l'iodure de sodium dans un solvant en vue d'effectuer les réactions suivantes : (1) ouvrir le cycle du composé de la formule (II) et (2) introduire un ion I provenant dudit iodure de sodium sur la quatrième position de l'intermédiare au cycle ouvert ainsi obtenu du composé de la formule (II) et mettre en contact l'intermédiaire au cycle ouvert dans lequel a été introduit l'ion I ainsi obtenu avec un alkylalcool comportant de 1 à 10 atomes de carbone afin d'introduire un groupe alkyle provenant dudit radical alkyle dans la partie carbonyloxylée dudit intermédiaire au cycle ouvert dans lequel a été introduit l'ion I.